Docket No.: 2815-0335PUS1
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Bjarne H. DAHL et al.

Application No.: 10/561,189 | Confirmation No.: 3923

Filed: December 16, 2005 | Art Unit: 1626

For: DIPHENYLUREA DERIVATIVES AND THEIR USE AS CHLORIDE CHANNEL BLOCKERS | Examiner: S. L. Chung

APPEAL BRIEF

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Madam:

As required under 37 C.F.R. § 41.37(a), this brief is filed subsequent to the Notice of Appeal filed in this case on July 20, 2009, and is in furtherance of said Notice of Appeal. This Appeal Brief is respectfully submitted in response to the final rejection of claims 9, 10 and 14-16 dated February 18, 2009.

The fees required under 37 C.F.R. § 41.20(b)(2) for filing of this Appeal Brief are addressed in the accompanying TRANSMITTAL OF APPEAL BRIEF.

Table of Contents

This brief contains items under the following headings as required by 37 C.F.R. § 41.37 and M.P.E.P. § 1206:

I. REAL PARTY IN INTEREST

The real party in interest (owner of all right and title in the claimed invention) for this appeal is:

NEUROSEARCH A/S, 93 Pederstrupvej, Ballerup, Denmark, DK-2750, as evidenced by the assignment recorded with the USPTO at Reel/Frame 017389/0337.

II. RELATED APPEALS AND INTERFERENCES

There are no pending Appeals or Interferences related to the present application known to Appellants or Appellants' Legal Representatives.

III. STATUS OF CLAIMS

Claims 9-10 and 14-16 are currently pending and rejected. Claims 1-8 and 11-13 have been previously cancelled. This is an appeal from the Final Rejection of claims 9-10 and 14-16.

IV. STATUS OF AMENDMENTS

An After-Final Amendment was filed on May 18, 2009. This amendment was entered into the record. The status of amendments is as displayed in the Claims Appendix attached hereto.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The present invention, as defined in independent claim 9, is directed to a chemical compound (each compound is supported by the specification, as noted below), which is:

N-(3,5-Difluoro-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-3′-trifluoromethyl-biphenyl-4-yl]-urea (*page 4, line 22; see also claim 14*);

N-(3,5-Dichloro-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-3′-trifluoromethyl-biphenyl-4-yl]-urea (*page 4, line 21; see also claim 15*);

N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-3′-trifluoromethyl-biphenyl-4-yl]-urea (*page 5, lines 27-28; see also claim 16*);

or a pharmaceutically acceptable salt thereof (*page 5, line 36*).

The present invention is also directed to a pharmaceutical composition comprising a therapeutically effective amount of the above-described compound, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, excipient or diluent *(see claim 10, and the specification at page 7, lines 29-33*).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The grounds of rejection to be reviewed on appeal are:

(1) whether claims 9-10 are obvious under the judicially created doctrine of obviousness-type double patenting over claims 1-15 of U.S. 6,297,261 (hereinafter "US '261");

(2) whether claims 9-10 are obvious under the judicially created doctrine of obviousness-type double patenting over claims 1-13 of U.S. 6,696,475 (hereinafter "US '475");

(3) whether claims 9-10 are obvious under the judicially created doctrine of obviousness-type double patenting over claims 12-20 of U.S. Patent Application No. 2006/0058395 (hereinafter "US '395"); and

(4) whether claims 9-10 are obvious under the judicially created doctrine of obviousness-type double patenting over claims 21-39 of U.S. Patent Application No. 2006/0160856 (hereinafter "US '856").

VII. ARGUMENT

Claims 9-10 stand rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-15 of US '261. Appellants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness of the invention as set forth in claims 9 and 10. Furthermore, the record provides objective evidence of unobviousness of the invention sufficient to rebut any possible case of *prima facie* obviousness that might be deemed established by the cited reference. Accordingly, the instant rejection of claims 9 and 10 over US '261 must be reversed.

Claims 9-10 also stand rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-13 of US '475. Appellants respectfully submit that the Examiner has failed to establish *prima facie* obviousness of the invention as set forth in claims 9 and 10. Furthermore, the record provides objective evidence of unobviousness of the invention sufficient to rebut any possible case of *prima facie* obviousness that might be deemed established by the cited reference. Accordingly, the instant rejection of claims 9 and 10 over US '475 must be reversed.

Claims 9-10 additionally stand rejected under the judicially created doctrine of obviousness-type double patenting over claims 12-20 of US '395. Appellants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness of the invention as set forth in claims 9 and 10. Furthermore, the record provides objective evidence of unobviousness of the invention sufficient to rebut any possible case of *prima facie*

obviousness that might be deemed established by the cited reference. Accordingly, the instant rejection of claims 9 and 10 over US '395 must be reversed.

Claims 9-10 further stand rejected under the judicially created doctrine of obviousness-type double patenting over claims 21-39 of US '856. Appellants respectfully submit that the Examiner has failed to establish *prima facie* obviousness of the invention as set forth in claims 9 and 10. Furthermore, the record provides objective evidence of unobviousness of the invention sufficient to rebut any possible case of *prima facie* obviousness that might be deemed established by the cited reference. Accordingly, the instant rejection of claims 9 and 10 over US '856 must be reversed.

Claims 14-16 have not been addressed by the Examiner. However, the Office Action Summary of February 18, 2009 identifies these claims as rejected. Appellants submit that these claims are allowable at least for the same reasons discussed herein with regards to claim 9, on which they depend.

VII (1). Double Patenting Issues – US '261

A. The Examiner fails to establish *prima facie* obviousness of the claimed invention, as described in claims 9 and 10.

To establish a *prima facie* case of obviousness, the Examiner must make the factual determinations set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). "[T]he examiner bears the initial burden, on review of the prior art or on any other ground, of presenting a *prima facie* case of unpatentability." *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992). A patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. *KSR Int'l Co. v Teleflex Inc.*, 82 USPQ 2d 1385 (U.S. 2007). There must be a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. *Id.* The Supreme Court of the United States has recently held that the "teaching, suggestion, motivation test" is a valid test for obviousness, albeit one which cannot be too rigidly applied. *Id.* "[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *Id.* (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)). "On appeal to the Board, an applicant can overcome a rejection [under § 103] by showing insufficient evidence of *prima facie* obviousness or by rebutting the *prima facie* case with evidence of secondary indicia of nonobviousness." *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) (quoting *In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998)).

1. The Examiner's statement of the rejection

The Examiner asserts that the presently claimed compounds are found in the genus and/or species claimed in, for example, claim 3 of US '261 at col. 17, lines 15-16 (see Office Action of February 18, 2009 at page 3, lines 5-6).

2. The cited reference fails to teach or suggest all of the features of the claimed invention.

The cited reference fails to disclose or suggest the presently claimed compounds. Claim 3 of US '261, which the Examiner alleges includes the claimed compound, is directed, in part, to a compound selected from a group including 3-Trifluoromethylphenyl-4-biphenylyl-2-(3-oxo-1,2-dihydro-1, 2, 4-triazol-1-yl) phenyl urea (relevant portion of claim 3 identified by the Examiner).

However, US '261 fails to teach or suggest a compound as claimed, which is one of N-(3,5-Difluoro-phenyl)-N′-[3-(1H-tetrazol-5-yl)-3′-trifluoromethyl-biphenyl-4-yl]-urea, N-(3,5-Dichloro-phenyl)-N′-[3-(1H-tetrazol-5-yl)-3′-trifluoromethyl-biphenyl-4-yl]-urea, N-(3,5-Bis-trifluoromethyl-phenyl)-N′-[3-(1H-tetrazol-5-yl)-3′-trifluoromethyl-biphenyl-4-yl]-urea, or a pharmaceutically acceptable salt thereof. Appellants submit that US '261 fails to teach or suggest a compound having a -[3-(1H-tetrazol-5-yl)- group therein, as presently claimed.

3. The evidence of superior and unexpected results in the record rebuts any prima facie case of obviousness arguably established by the Examiner

As noted above, Appellants submit that US '261 fails to teach or suggest a compound as presently claimed. For this reason alone, the outstanding rejection of claims 9 and 10 is improper and should be withdrawn.

Additionally, Appellants submit that the evidence of superior and unexpected results of record rebuts any *prima facie* case of obviousness arguably established by the Examiner. Appellants further submit that the Examiner has failed to accord this evidence sufficient weight.

As demonstrated by the Declaration of Palle Christophersen, submitted under 37 C.F.R. 1.132 on November 17, 2008, a copy of which is attached hereto, the present compound exhibits unexpected advantageous properties over the compounds of the prior art of record, as evidenced by a K_D value that is over 100X lower than that of the prior art.

The Examiner has taken the position that a K_D value of over 100 times lower than that of the prior art compounds is not an unexpected result (see Office Action of February 18, 2009 at page 3, lines 13-18). However, Appellants submit that one skilled in the art would have expected similar compounds to have similar properties and activity. Thus, a 100X difference in K_D is clearly unexpected. As discussed in the Declaration of November 17, 2008, the compounds of the instant invention show a highly improved effect as blockers of VRAC (volume regulated anion channel), as compared to prior art compounds. This effect is evidenced by the much lower K_D value exhibited by the presently claimed compounds.

The Examiner also alleges that the results of the November 17, 2008 Declaration are not persuasive because "there was no side by side comparison between all of the compounds of the cited references" (see Office Action of February 18, 2009 at page 3, lines 11-13). Appellants note that the Examiner's assertion that Applicants must compare the present invention to all of the compounds of the cited references is incorrect. Under U.S. patent laws, Appellants only need to compare the closest prior art compound to the claimed compounds. Appellants submit that the closest prior art is WO 2004/022529, disclosing diarylurea derivatives and their use as chloride channel blockers. Appellants have submitted sufficient experimental data which compares the present application with the closest prior art. As such, Appellants have fulfilled their burden, and have clearly established superior and unexpected results.

For this additional reason, the Board should reverse the Examiner's rejection.

B. Conclusion

In conclusion, Appellants respectfully submit that it has been shown that the Examiner has failed to properly establish that the rejected claims are *prima facie* obvious under the judicially created doctrine of obviousness-type double patenting over claims 1-15 of US '261.

Thus, for the reasons advanced above, it is respectfully submitted that claims 9 and 10 are allowable. Favorable reconsideration and reversal of the Examiner's rejection of claims 9 and 10 under the judicially created doctrine of obviousness-type double patenting by the Honorable Board of Patent Appeals and Interferences, are respectfully solicited.

VII (2). Double Patenting Issues – US '475

A. The Examiner fails to establish *prima facie* obviousness of the claimed invention, as described in claims 9 and 10.

1. The Examiner's statement of the rejection

The Examiner asserts that the presently claimed compounds are found in the genus and/or species claimed in, for example, claim 6 of US '475 at col. 29, lines 48-50 and 55-57 (see Office Action of February 18, 2009 at page 3, line 7).

2. The cited reference fails to teach or suggest all of the features of the claimed invention.

The cited reference fails to disclose or suggest the presently claimed compounds. The relevant portion of claim 6 of US '475, which the Examiner alleges includes the claimed compound, is directed to a compound, such as N-(3-trifluoromethylphenyl)+N'-(4'-(N, N-dimethylsulfamoyl) -2(1-H-tetrazol-5-yl)-4-biphenyl) urea, and N-(3-trifluoromethylphenyl) – N'- (4'-(N, N-dimethylcarbamoyl)-2-(1-H-tetrazol-5-yl)-4-biphenyl) urea.

However, US '475 fails to teach or suggest a compound as claimed, which is one of N-(3,5-Difluoro-phenyl)-N′-[3-(1H-tetrazol-5-yl)-3′-trifluoromethyl-biphenyl-4-yl]-urea, N-(3,5-Dichloro-phenyl)-N′-[3-(1H-tetrazol-5-yl)-3′-trifluoromethyl-biphenyl-4-yl]-urea, N-(3,5-Bis-trifluoromethyl-phenyl)-N′-[3-(1H-tetrazol-5-yl)-3′-trifluoromethyl-biphenyl-4-yl]-urea, or a pharmaceutically acceptable salt thereof. Appellants submit that US '475 fails to

teach or suggest a compound having a -[3-(1H-tetrazol-5-yl)- group therein, as presently claimed.

3. The evidence of superior and unexpected results in the record rebuts any prima facie case of obviousness arguably established by the Examiner

As noted above, Appellants submit that US '475 fails to teach or suggest a compound as presently claimed. For this reason alone, the outstanding rejection of claims 9 and 10 is improper.

Moreover, as discussed in the preceding section, Appellants submit that the evidence of superior and unexpected results of record rebuts any *prima facie* case of obviousness arguably established by the Examiner. As demonstrated by the Declaration under 37 C.F.R. 1.132 filed on November 17, 2008, the present compound exhibits unexpected advantageous properties over the compounds of the prior art of record, as evidenced by a K_D value that is over 100X lower than that of the prior art.

Appellants have clearly established superior and unexpected results. For this additional reason, the Board should reverse the Examiner's rejection.

B. Conclusion

In conclusion, Appellants respectfully submit that it has been shown that the Examiner has failed to properly establish that the rejected claims are *prima facie* obvious under the judicially created doctrine of obviousness-type double patenting over claims 1-13 of US '475.

Thus, for the reasons advanced above, it is respectfully submitted that claims 9 and 10 are allowable. Favorable reconsideration and reversal of the Examiner's rejection of claims 9 and 10 under the judicially created doctrine of obviousness-type double patenting by the Honorable Board of Patent Appeals and Interferences, are respectfully solicited.

VII (3). Double Patenting Issues – US '395

A. The Examiner fails to establish *prima facie* obviousness of the claimed invention, as described in claims 9 and 10.

1. The Examiner's statement of the rejection

The Examiner asserts that the presently claimed compounds are found in the genus and/or species claimed in, for example, claim 20 of US '395 at page 14 (see Office Action of February 18, 2009 at page 3, lines 7-8).

2. The cited reference fails to teach or suggest all of the features of the claimed invention.

The cited reference fails to disclose or suggest the presently claimed compounds. The relevant portion of claim 20 of US '395, which the Examiner alleges includes the claimed compound, is directed to 3'-(1-H-tetrazol-5-yl)-4'-[3-(3-trifluoromethyl-phenyl)-ureido]-biphenyl-4-carboxylic acid.

However, US '395 fails to teach or suggest a compound as claimed, which is one of N-(3,5-Difluoro-phenyl)-N′-[3-(1H-tetrazol-5-yl)-3′-trifluoromethyl-biphenyl-4-yl]-urea, N-(3,5-Dichloro-phenyl)-N′-[3-(1H-tetrazol-5-yl)-3′-trifluoromethyl-biphenyl-4-yl]-urea, N-(3,5-Bis-trifluoromethyl-phenyl)-N′-[3-(1H-tetrazol-5-yl)-3′-trifluoromethyl-biphenyl-4-yl]-urea, or a pharmaceutically acceptable salt thereof.

3. The evidence of superior and unexpected results in the record rebuts any prima facie case of obviousness arguably established by the Examiner

As noted above, Appellants submit that US '395 fails to teach or suggest a compound as presently claimed. For this reason alone, the outstanding rejection of claims 9 and 10 is improper.

Moreover, as discussed in the preceding section, Appellants submit that the evidence of superior and unexpected results of record rebuts any *prima facie* case of obviousness arguably established by the Examiner. As demonstrated by the Declaration under 37 C.F.R. 1.132 filed on November 17, 2008, the present compound exhibits unexpected advantageous properties over the compounds of the prior art of record.

Appellants have clearly established superior and unexpected results. For this additional reason, the Board should reverse the Examiner's rejection.

B. Conclusion

In conclusion, Appellants respectfully submit that it has been shown that the Examiner has failed to properly establish that the rejected claims are *prima facie* obvious under the judicially created doctrine of obviousness-type double patenting over claims 12-20 of US '395.

Thus, for the reasons advanced above, it is respectfully submitted that claims 9 and 10 are allowable. Favorable reconsideration and reversal of the Examiner's rejection of claims 9 and 10 under the judicially created doctrine of obviousness-type double patenting by the Honorable Board of Patent Appeals and Interferences, are respectfully solicited.

VII (3). Double Patenting Issues – US '856

A. The Examiner fails to establish *prima facie* obviousness of the claimed invention, as described in claims 9 and 10.

1. The Examiner's statement of the rejection

The Examiner asserts that the presently claimed compounds are found in the genus and/or species claimed in, for example, claim 33 of US '856 at pages 28-29 (see Office Action of February 18, 2009 at page 3, lines 7-8).

2. The cited reference fails to teach or suggest all of the features of the claimed invention.

The cited reference fails to disclose or suggest the presently claimed compounds. The relevant portion of claim 33 of US '856, which the Examiner alleges includes the claimed compound, is directed to a compound, such as N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[2-(1H-tetrazol-5-yl)-biphenyl-4- -yl-4'-sulfonic acid-dimethylamide]urea, or N-(4-Chloro-3-trifluoromethyl-phenyl)-N'-[4'-(N", N"-dimethyl-1-carbonyl)-3-1-(H-tetrazol-5-yl)-biphenyl-4-yl]urea.

However, US '856 fails to teach or suggest a compound as claimed, which is one of N-(3,5-Difluoro-phenyl)-N′-[3-(1H-tetrazol-5-yl)-3′-trifluoromethyl-biphenyl-4-yl]-urea, N-(3,5-Dichloro-phenyl)-N′-[3-(1H-tetrazol-5-yl)-3′-trifluoromethyl-biphenyl-4-yl]-urea, N-(3,5-Bis-trifluoromethyl-phenyl)-N′-[3-(1H-tetrazol-5-yl)-3′-trifluoromethyl-biphenyl-4-yl]-urea, or a pharmaceutically acceptable salt thereof.

3. The evidence of superior and unexpected results in the record rebuts any prima facie case of obviousness arguably established by the Examiner

As noted above, Appellants submit that US '856 fails to teach or suggest a compound as presently claimed. For this reason alone, the outstanding rejection of claims 9 and 10 is improper.

Moreover, as discussed in the preceding section, Appellants submit that the evidence of superior and unexpected results of record rebuts any *prima facie* case of obviousness

arguably established by the Examiner. For this additional reason, the Board should reverse the Examiner's rejection.

B. Conclusion

In conclusion, Appellants respectfully submit that it has been shown that the Examiner has failed to properly establish that the rejected claims are *prima facie* obvious under the judicially created doctrine of obviousness-type double patenting over claims 21-39 of US '856.

Thus, for the reasons advanced above, it is respectfully submitted that claims 9 and 10 are allowable. Favorable reconsideration and reversal of the Examiner's rejection of claims 9 and 10 under the judicially created doctrine of obviousness-type double patenting by the Honorable Board of Patent Appeals and Interferences, are respectfully solicited.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Dated: SEP 21 2009

Respectfully submitted,

By _____
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VIII. CLAIMS APPENDIX

The claims involved in the Appeal of Application Serial No. 10/561,189 are as follows:

9. A chemical compound compound, which is:

N-(3,5-Difluoro-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-3′-trifluoromethyl-biphenyl-4-yl]-urea;

N-(3,5-Dichloro-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-3′-trifluoromethyl-biphenyl-4-yl]-urea;

N-(3,5-Bis-trifluoromethyl-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-3′-trifluoromethyl-biphenyl-4-yl]-urea;

or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 9, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, excipient or diluent.

14. The compound of claim 9, which is: *N*-(3,5-Difluoro-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-3'-trifluoromethyl-biphenyl-4-yl]-urea; or a pharmaceutically acceptable salt thereof.

15. The compound of claim 9, which is: *N*-(3,5-Dichloro-phenyl)-*N*'-[3-(1*H*-tetrazol-5-yl)-3'-trifluoromethyl-biphenyl-4-yl]-urea; or a pharmaceutically acceptable salt thereof.

16. The compound of claim 9, which is: *N*-(3,5-Bis-trifluoromethyl-phenyl)-*N*'-[3-(1*H*-tetrazol-5-yl)-3'-trifluoromethyl-biphenyl-4-yl]-urea; or a pharmaceutically acceptable salt thereof.

IX. EVIDENCE APPENDIX

Declaration of Palle Christophersen, submitted under 37 C.F.R. §1.132 (entered in the record on November 17, 2008).

X. RELATED PROCEEDINGS APPENDIX

None.

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(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Bjarne H. DAHL et al.

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Filed: December 16, 2005 | Art Unit: 1626

For: DIPHENYLUREA DERIVATIVES AND THEIR USE AS CHLORIDE CHANNEL BLOCKERS | Examiner: S. L. Chung

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Palle Christophersen, so hereby declare the following:

I am the Vice President and Director of In Vitro Pharmacology at NeuroSearch A/S of Ballerup, Denmark.

A copy of my curriculum vitae is attached hereto.

I have read and understand the specification and claims to the above-identified application and the outstanding Office Action of July 15, 2008 (hereinafter "Office Action"), in particular the rejections over obviousness-type double patenting over Claims 1-15 of USP 6,297,261; Claims 1-13 of USP 6,696,475; Claims 12-20 of published application No. 2006/0058395 and Claims 21-39 of published application No. 2006/0160856.

Attached hereto as Exhibit A is data that shows that the compounds of the instant invention possess unexpected advantageous properties compared to the prior art compounds, as evidenced by a K_D value more than 100X lower than that of the prior art compounds. With the

attached data, Compound A is a claimed compound of the instant invention, i.e. *N*-(3,5-Dichloro-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-3'-trifluoromethyl-biphenyl-4-yl]-urea. Compound B is *N*-(3,5-Dichloro-phenyl)-*N'*-[4'-carboxamid-2-(1H-tetrazol-5-yl)-4-biphenyl urea from US 2006/0160856 and the Compounds C, D and E are respectively, N-(3-Trifluoromethylphenyl)-N'-(4'-carboxy-2-(1-H-tetrazol-5-yl)-4-biphenyl) urea; 3-Trifluoromethylphenyl-4-phenyl-2-(5-tetrazolyl)phenyl urea and 3-Trifluoromethylphenyl-4-(4-aminocarbonylphenyl)-2-(5-tetrazolyl)phenyl urea, which are all disclosed in USP 6,297,261, USP 6,696,475, and US 2006/0058395. Exhibit A further discusses the comparative study done with these compounds.

I hereby declare that all statements made herein of any own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001, of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: 13-11-2008

Palle Christophersen

Palle Christophersen, PhD

Enclosures: Exhibit A: Comparative data

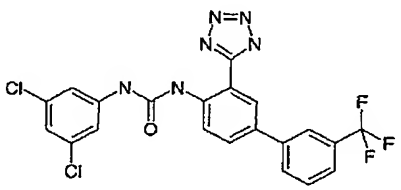
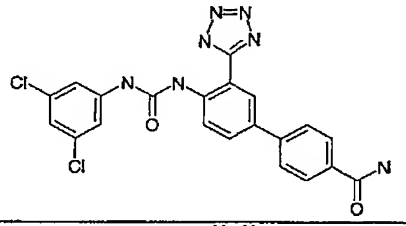
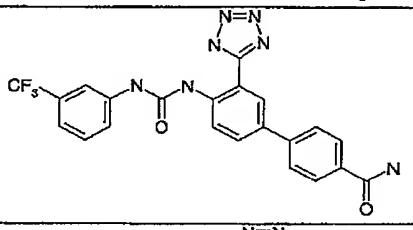
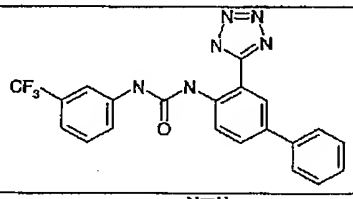
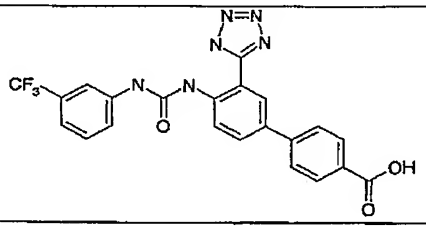
EXHIBIT A
Comparative Data

In this exhibit the effect of the compound of the invention *N*-(3,5-dichloro-phenyl)-*N'*-[3-(1*H*-tetrazol-5-yl)-3'-trifluoromethyl-biphenyl-4-yl]-urea (compound A, 4th compound on page 19 of the specification) and the prior art compounds *N*-(3,5-dichloro-phenyl)-*N'*-[4'-carboxamide-2-(1*H*-tetrazol-5-yl)-4-biphenyl] urea (compound B; of WO 2004/022529) and 3-trifluoromethylphenyl-4-(4-aminocarbonylphenyl)-2-(5-tetrazolyl)phenyl urea, 3-trifluoromethylphenyl-4-phenyl-2-(5-tetrazolyl)phenyl urea, and *N*-(3-trifluoromethylphenyl)-*N'*-(4'-carboxy-2-(1*H*-tetrazol-5-yl)-4-biphenyl) urea (compounds C-E; all of US 2002-037905) on the Volume Regulated Anion Channel (VRAC) was tested by the whole cell patch clamp technique using Human Embryonic Kidney cells (HEK293) as described in Helix et al, 2003.

In short, VRAC was activated by swelling of the cell in hypotonic (75 % tonicity) extracellular salt solution and the anion current elicited by voltage ramps was measured vs. time. After stabilization of the current the compounds (A and B, respectively) were added to the extracellular solution and the time dependent block was followed for calculation of the K_D values.

The values obtained are shown in Table 1:

Table 1

Compound	Structure	K_D value
Compound A of the invention 4th compound on page 19 of the specification		0.095 µM
Compound B, 5th compound on page 45 of the specification of WO 2004/022529		> 1 µM
Compound C, 6th last compound of Example 2, right column on page 13 of the specification of US 2002/0037905		> 1 µM
Compound D, 4th compound of Example 2, right column on page 13 of US 2002-0037905		> 1 µM
Compound E, 15th compound of Example 1, right column on page 12 of US 2002-0037905		> 1 µM

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1989-1991	Scientist at Center for Biomembranes, University of Århus.
1991-	Research scientist, electrophysiology, NeuroSearch A/S
1995-2002	Project manager, NeuroSearch A/S
2002-	Scientific Officer, Ion Channels, NeuroSearch A/S,
2004-	Director of In Vitro Pharmacology, NeuroSearch A/S
2006-	Vice President, NeuroSearch A/S

Number of publications in peer reviewed journals and books: 49
Accepted manuscripts: 2
Submitted manuscripts: 2
Number of patent publications: 61

SELECTED PUBLICATIONS

Ulrik S. Sørensen, Dorte Strøbæk, **Palle Christophersen**, Charlotte Hougaard, Marianne L. Jensen, Elsebet Ø. Nielsen, Dan Peters, and Lene Teuber. Synthesis and Structure-Activity Relationship Studies of 2-(N-Substituted)-aminobenzimidazoles as Potent Negative Gating Modulators of Small Conductance Ca^{2+}-Activated K^+ Channels. J Med Chem, epub ahead of print.

Jacobsen JP, Weikop P, Hansen HH, Mikkelsen JD, Redrobe JP, Holst D, Bond CT, Adelman JP, **Christophersen P**, Mirza NR. (2008) SK3 K^+ channel-deficient mice have enhanced dopamine and serotonin release and altered emotional behaviors. Genes Brain Behav, epub ahead of print.

Hougaard C, Eriksen BL, Jorgensen S, Johansen TH, Dyhring T, Madsen LS, Strobaek D, **Christophersen P**. Selective positive modulation of the SK3 and SK2 subtypes of small conductance Ca^{2+}-activated K^+ channels. Br J Pharmacol. 2007.

Strobaek D, Hougaard C, Johansen TH, Sorensen US, Nielsen EO, Nielsen KS, Taylor RD, Pedarzani P, **Christophersen P.** (2006) Inhibitory gating modulation of small conductance Ca2+-activated K+ channels by the synthetic compound (R)-N-(benzimidazol-2-yl)-1,2,3,4-tetrahydro-1-naphtylamine (NS8593) reduces afterhyperpolarizing current in hippocampal CA1 neurons. Mol Pharmacol. 70(5):1771-82.

Pedarzani P, McCutcheon JE, Rogge G, Jensen BS, **Christophersen P**, Hougaard C, Strobaek D, Stocker M. (2005) Specific enhancement of SK channel activity selectively potentiates the afterhyperpolarizing current I(AHP) and modulates the firing properties of hippocampal pyramidal neurons. J Biol Chem. 280(50):41404-11.

Schroder RL, Strobaek D, Olesen SP, Christophersen P. (2003) Voltage-independent KCNQ4 currents induced by (+/-)BMS-204352. Pflugers Arch. 446(5):607-16.

Jensen BS, Strobaek D, Olesen SP, **Christophersen P.** (2001) The Ca^{2+}-activated K^+ channel of intermediate conductance: a molecular target for novel treatments, Curr Drug Targets. 2(4):401-22. Review

Bennekou P, de Franceschi L, Pedersen O, Lian L, Asakura T, Evans G, Brugnara C, **Christophersen P.** (2001) Treatment with NS3623, a novel Cl-conductance blocker, ameliorates erythrocyte dehydration in transgenic SAD mice: a possible new therapeutic approach for sickle cell disease. Blood. 97(5):1451-7.

Strobaek D, Jorgensen TD, **Christophersen P**, Ahring PK, Olesen SP. (2000) Pharmacological characterization of small-conductance Ca^{2+}-activated K^+ channels stably expressed in HEK 293 cells. Br J Pharmacol. 129(5):991-9.

Pedersen KA, Schroder RL, Skaaning-Jensen B, Strobaek D, Olesen SP, **Christophersen P** (1999) Activation of the human intermediate-conductance Ca^{2+}-activated K^+ channel by 1-ethyl-2-benzimidazolinone is strongly Ca^{2+}-dependent. Biochim Biophys Acta. 1420(1-2):231-40

Christophersen P (1991) Ca^{2+}-activated K^+ channel from human erythrocyte membranes: single channel rectification and selectivity. J Membr Biol. 119(1):75-83.

Vestergaard-Bogind B, Stampe P, **Christophersen P** (1985) Single-file diffusion through the Ca^{2+}-activated K^+ channel of human red cells. J Membr Biol. 88(1):67-75.